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Primer

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Invasive candidiasis

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Abstract

Invasive candidiasis is an important fungal disease caused by *Candida albicans* and, increasingly, non-*albicans Candida* pathogens. Invasive *Candida* infections originate most frequently from endogenous human reservoirs and are triggered by impaired host defences. Signs and symptoms of invasive candidiasis are non-specific; candidaemia is the most diagnosed manifestation, with disseminated candidiasis affecting single or multiple organs. Diagnosis poses many challenges, and conventional culture techniques are frequently supplemented by non-culture-based assays. The attributable mortality from candidaemia and disseminated infections is ~30%. Fluconazole resistance is a concern for *Nakaseomyces glabratus*, *Candida parapsilosis*, and *Candida auris* and less so in *Candida tropicalis* infection; acquired echinocandin resistance remains uncommon. The epidemiology of invasive candidiasis varies in different geographical areas and within various patient populations. Risk factors include intensive care unit stay, central venous catheter use, broad-spectrum antibiotics use, abdominal surgery and immune suppression. Early antifungal treatment and central venous catheter removal form the cornerstones to decrease mortality. The landscape of novel therapeutics is growing; however, the application of new drugs requires careful selection of eligible patients as the spectrum of activity is limited to a few fungal species. Unanswered questions and knowledge gaps define future research priorities and a personalized approach to diagnosis and treatment of invasive candidiasis is of paramount importance.

Sections

Introduction

Epidemiology

Mechanisms/pathophysiology

Diagnosis, screening and prevention

Management

Quality of life

Outlook

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Introduction

Fungi are a heterogeneous group of eukaryotes and are one of the most widely distributed organisms on earth[1]. In the medical setting, the simple categorization between yeasts (that is, *Candida* species) and moulds (that is, *Aspergillus* species) is most practical[2] in guiding clinician decision-making on which therapy to use. Under the microscope, yeasts generally appear as single cells (budding) and moulds as hyphal (filamentous) elements. *Candida* spp. are yeasts capable of causing a wide spectrum of infections, ranging from mild to severe disease[3].

Invasive candidiasis encompasses a variety of disorders, may affect any organ, and refers to deep-seated or disseminated infections (systemic candidiasis), which usually affect patients with impaired host defence mechanisms[3,4]. The most serious infection is candidaemia, which refers to *Candida* bloodstream infections (BSIs). Overall, disease may be acute or chronic, the latter usually occurring in those with significant comorbidities[4]. *Candida*-related infections rank among the 10 most frequently isolated pathogens in intensive care units (ICUs)[5] or in immunocompromised patients[5] and cause up to 10% of hospital-acquired BSIs[6], surpassing some common bacterial organisms such as *Pseudomonas aeruginosa*[7]. *Candida albicans* is the medically most prevalent causative species; nevertheless, non-*albicans* *Candida* infections continue to increase, with multidrug-resistant species, including *Candida parapsilosis*, *Nakaseomyces glabratus* (formerly *Candida glabrata*) and *Candida auris*, being of particular concern[8,9] (Box 1).

The diagnosis and management of invasive candidiasis is a clinical challenge as traditional diagnostics, such as culture, lack high sensitivity and/or specificity[10]; antifungal treatment decisions and dosing may be complex simply because of intrinsic and/or acquired resistance in *Candida* species, drug–drug interactions, toxicities and unpredictable pharmacokinetics[4]. In the past year, new antifungal drug classes have become available for the treatment of *Candida* infections.

This Primer provides a summary of the epidemiology, pathophysiology, diagnosis and treatment of invasive candidiasis, offering a comprehensive overview to health-care providers and researchers from multiple disciplines. We focus on medical data published within the past 5 years. No in-depth guidance for diagnostic procedures, including imaging, disease management or molecular-based resistance detection, is addressed herein as these topics have been reviewed elsewhere.

Epidemiology

Incidence and prevalence rates

The incidence and prevalence of invasive candidiasis are influenced by various factors such as geographical region, health-care system, patient demographics and environmental factors. Community-acquired cases account for less than a quarter of candidaemia cases[11], with incidence rates of ~4 per 100,000 in the general population in high-income countries[11,12] and *Candida* species accounting for ~3% of all BSIs[13]. The burden of disease is markedly higher in hospitalized patients worldwide (~100 per 100,000 admissions)[14–16], with the highest incidence in patients in the ICU, reaching 5.5–7 episodes per 1,000 ICU admissions[12,17,18]. Neonates, especially if born preterm, are also at a higher risk of candidaemia, with an incidence of up to 12 per 100,000 births in the USA[19]. Consistent with other age groups, most of these neonates are in the ICU, have a central venous catheter and receive parenteral nutrition[19,20]. Most available data regard candidaemia; however, the incidence of invasive abdominal candidiasis with no or only transient candidaemia is likely much higher[21].

Risk factors

Epidemiological risk factors. Epidemiological factors that influence the risk of invasive candidiasis include ethnic, racial, gender-specific and sex-specific disparities. Accordingly, black patients are in the USA often disproportionally affected (2.3 times higher incidence)[22], presumably as a consequence of socio-economic factors, including poor access to health-care services and higher rates of underlying diseases that compromise the immune response such as diabetes mellitus, chronic renal disease requiring haemodialysis and liver disease[23,24]. Male sex is often reported as a risk factor for invasive candidiasis[14,22], with an incidence of ~8 per 100,000 in male patients compared with 6 per 100,000 in female patients[25]. While biological differences in steroid hormones and sex-specific immune responses[26] may influence the susceptibility to various fungal diseases, lifestyle choices and gender differences in seeking and receiving health care are likely contributory factors; however, these are difficult to adequately assess[26]. In several population-based studies, incidence was highest among adults aged ≥65 years (up to 25.5 per 100,000), followed by infants (up to 15.8 per 100,000)[11,22,25]. For older people, this can be attributed to comorbidities predisposing to various opportunistic infections increasing with age[27], while for neonates and especially those with preterm births, the underdeveloped immune system[28] and incomplete development of epithelial barriers, coupled with invasive critical care medicine, predispose to infection[29].

Medical risk factors. Patients after stem cell or solid organ transplantation are at increased risk[30], with up to 5.5% of patients developing candidaemia following transplantation[31]. Haematological or oncological diseases, ICU admission, and surgery are the most common risk factors for invasive candidiasis[32]. These reflect the underlying mechanisms for developing invasive candidiasis, consisting of an immunocompromised host, the disruption of epithelial barriers (for instance, by medical devices or mucosal inflammation) and increased colonization with yeast species, most commonly due to antibiotic treatment (Box 2). Due to several risk factors for fungal infections, including treatment modalities, critically ill patients with COVID-19 are at high risk of developing invasive candidiasis[33].

Additionally, breaches in skin or mucosal barriers, as observed in extensive full-thickness burns, gastrointestinal perforations, acute or necrotizing pancreatitis, gastrointestinal surgery, mucositis induced by chemotherapy, the presence of indwelling intravascular catheters, and urinary tract instrumentation, subsequently increase the likelihood of translocation of the *Candida* species into the bloodstream. Patients reliant on total parenteral nutrition or those with indwelling prosthetic materials, such as haemodialysis or peritoneal catheters, left ventricular assist devices, ventriculoperitoneal shunts, or external ventricular drains, are also at elevated risk of invasive disease owing to the loss of integrity of the normal anatomical defences. Intrinsic or acquired immunosuppression significantly heightens susceptibility to invasive candidiasis. Patients at the extremes of age, those with diabetes mellitus and people with severe viral infections, like COVID-19, have a compromised or dysfunctional immune response, providing an environment for *Candida* species to thrive and invade[34]. Profound and prolonged neutropenia, with an absolute neutrophil count below 500/μl, specifically weakens innate immune defences, making it easier for *Candida* species to invade. Solid organ transplant and haematopoietic stem cell transplant recipients, along with patients receiving immunosuppressive treatments, including corticosteroids, are also particularly vulnerable. Genetic factors are thought to be involved;

Box 1

The six most clinically relevant *Candida* species

Candida albicans
- 90% of humans are colonized
- Most important species in human medicine
- Can affect nearly all organs; candidaemia is the most prevalent clinical presentation
- Less involved in otomycosis and outbreaks
- Majority of infections are from endogenous sources
- Resistance is rare

***Candida parapsilosis* species complex**
- 10% of adults are colonized
- The majority of infections are exogenous
- Affects neonates and the older population
- Associated with total parenteral nutrition and poor hand hygiene
- Strong biofilm producer in vivo
- Increased fluconazole resistance, tendency to clonal outbreaks
- Prevalent in southern Europe and southern Africa

***Pichia kudriavzevii* (formerly *Candida krusei*)**
- Transient inhabitant of mucosal membranes in healthy individuals
- Widely distributed in nature (vegetables and fruits)
- Affects individuals with haematological malignancies and transplant recipients
- Intrinsically resistant to fluconazole, rapidly acquiring multidrug resistance (echinocandins and azoles)
- Highest frequency of isolation in Europe (Czech Republic, 7.6%) and North America and lowest in Indonesia, South Korea and Thailand

***Nakaseomyces glabratus* (formerly *Candida glabrata*)**
- Colonizer of the healthy microbial flora
- Infection source is generally endogenous, some studies found horizontal transfer for this species
- Widely distributed in the environment (water and soil)
- Second most important species in the USA and north-western Europe, where infection leads to substantial morbidity and mortality (40–60%)
- Rapidly acquires resistance to echinocandins, high frequency of azole resistance

Candida tropicalis
- Can be found on skin, nails and mucosa
- Widely distributed in the environment (soil, water, Amazon forest)
- Most important species in India and Pakistan, second in Latin America; in the northern hemisphere, patients with cancer are at risk
- Resistance to fluconazole, mainly in India followed by Turkey, Spain and Algeria
- Strong biofilm producer
- Horizontally transferred in hospitals

Candida auris
- Skin colonizer, with ~10% of colonized people going on to develop invasive infection
- Infection source is either endogenous (skin) or exogenous from the immediate contaminated health-care environment
- Associated with large health-care-related outbreaks
- Rapidly becoming a major pathogen causing invasive infection, particularly in low-income and middle-income countries
- Clade-specific resistance patterns with clade I more resistant than clade III and IV (clades II and V are rarely associated with invasive infection)

Data compiled from refs. 47,131,135,188–190.

for example, mutations in immune-related genes might predispose individuals to invasive *Candida* infections[35].

Species distribution

The genus *Candida* is a heterogeneous collection of species with different phylogenetic backgrounds. Many *Candida* species infecting humans belong to the so-called CUG clade, in which the CUG codon has been reassigned to code for a different amino acid (that is, serine) than generally applied in the universal genetic code (that is, leucine)[36]. Some important exceptions include the common species *N. glabratus*, which is more closely related to *Saccharomyces cerevisiae*, and *Pichia kudriavzevii* (formerly *Candida krusei*)[37]. As a result, these diverse species have evolved distinct virulence factors, exhibit heterogeneous behaviour within the human host and display varying inherent susceptibilities to antifungal agents. Consequently, diagnostic species identification gives important information about the probability of acquired or intrinsic antifungal resistance as well as the expected outcome of infection. Over the past 25 years, a steady decrease in the abundance of *C. albicans* compared with non-*albicans Candida* species has occurred; however, *C. albicans* remains the most common species worldwide[9].

One of the primary distinctions among the most prevalent species is that *N. glabrata* is more frequently isolated in older patients (22% in patients ≥70 years versus 6% in patients aged ≤1–19 years)[9], resulting in a higher geographical distribution in high-income countries and regions with ageing populations[9]. Conversely, the *C. parapsilosis* species complex frequently infects neonates and infants (28–42% of candidaemias in these age groups)[38].

C. auris[39], which was first described in 2009 and comprises six known clades, has so far not reached a mentionable prevalence in global surveillance programmes[9] and, in many countries, no or only a few cases have been recorded[12]. However, its tendency to cause large hospital outbreaks[40] has the potential to change these numbers rapidly, as occurred, for example, in South Africa[15], India[18] and

Box 2

Risk factors for invasive candidiasis[4,21,89]

Proliferation of *Candida species* in skin or mucosal flora, with documented culture-based colonization at multiple body sites, can be risk factors when the following medical interventions are performed.

- Broad-spectrum antibiotics use
- Long-term stay in an acute-care facility or intensive care unit
- Mechanical ventilation

Breaches in skin or mucosal barriers, either related to an underlying condition or iatrogenic, can enable the *Candida* species to enter the body, examples are as follows.

- Extensive burns
- Gastrointestinal perforation
- Acute or necrotizing pancreatitis
- Gastrointestinal surgery
- Chemotherapy-induced mucositis
- Indwelling intravascular catheters
- Haemodialysis or peritoneal dialysis
- Total parenteral nutrition
- Indwelling prosthetic materials, including left ventricular assist devices, ventriculoperitoneal shunts or external ventricular drains
- Intravenous drug use
- Urinary tract instrumentation

Intrinsic or acquired immunosuppression, examples are as follows.

- Genetic susceptibility to invasive candidiasis by variations in immune-related genes
- Extremes of age (in particular, small, vulnerable newborns)
- Diabetes mellitus
- Viral infections such as COVID-19
- Profound and prolonged neutropenia
- Solid organ transplant and haematopoietic stem cell transplant recipients
- Immunosuppressive treatment, including corticosteroids
- Graft-versus-host disease

Lebanon[41]. In the latest European observational cohort study, *C. auris* was already among the six most commonly isolated species[32]. The wide geographical variation (Fig. 1) is influenced by demographics, with an ageing population in high-income countries compared with low-income and middle-income countries (LMICs), different health-care systems with varying strategies for antimicrobial treatment and prophylaxis, and heterogeneous proportions of vulnerable patient groups living with HIV, transplantations or oncological diseases[42]. Multicentre and nationwide studies published in the last 10 years from LMICs are scarce; however, the existing data suggest a different species distribution[15,43] with higher percentages of *C. parapsilosis* (up to 44% in South Africa)[15,20] and *C. auris* (up to 38% in Kenya)[44] than in high-income countries[45,46].

Drug resistance is a known and increasing threat in most infectious disease disciplines, and yeasts are no exception. Worrisome developments include the global spread of multidrug-resistant *C. auris*[39] and fluconazole-resistant *C. parapsilosis*[47], both causing large and long-lasting hospital outbreaks. Consistent with experimental data showing that virulence varies among the different species[48], disease outcome and crude mortality rates differ between *Candida* species[14,49]. Overall, candidaemia still has a high crude mortality of ~40%[32,49], defined as the overall death rate among infected patients. The attributable mortality, which refers to the deaths specifically caused by candidaemia, is ~27%[50], and the outcome largely depends on patient factors and the antifungal treatment strategy[50].

Mechanisms/pathophysiology

Unless otherwise stated, the focus of this section is *C. albicans*, which is the most common cause of invasive candidiasis[51]. The development of invasive candidiasis involves an interplay between the host and the pathogen[51,52].

Virulence factors

Several *Candida* virulence factors (molecules that assist in establishing an infection in its host) facilitate invasion, dissemination and seeding, or the establishment of infection, in organs. Some of these virulence factors are potential vaccination targets (Fig. 2).

Dimorphism. The ability of *C. albicans* to transition from a unicellular yeast form to hyphae is an integral factor in its pathogenicity[53]. Generally, the yeast form is associated with colonization and dissemination, while the hyphal form is linked to invasion and immune evasion[52]. Each morphological form possesses distinct surface molecules[53]. This dimorphic transition is primarily driven by the activation of the cyclic adenosine monophosphate (cAMP)-dependent and mitogen-activated protein kinase (MAPK) pathways in response to different environmental signals. These include the concentrations of certain molecules or stimuli such as carbon dioxide and N-acetylglucosamine for cAMP-dependent pathways and cell-wall damage, variations in temperature, and low nitrogen levels for MAPK-dependent pathways[54]. Notably, this transition is not employed by many *Candida* species. *C. tropicalis* and *C. parapsilosis* do exhibit a hyphal form but its role in invasive disease remains poorly understood[55].

Adhesion. The ability of *Candida* species to adhere to biotic or abiotic surfaces has a significant contribution to their virulence by enabling invasion and facilitating biofilm formation. This process relies on fungal surface proteins called adhesins, notably those belonging to the agglutinin-like sequence and hyphal wall protein families, which are proteins that have demonstrated the ability to interact with a broad range of molecules displayed on epithelial and endothelial cell surfaces[56]. The morphology-associated differential expression of these proteins is noteworthy as the presence of these morphologies in various environments necessitates an adaptability that enhances survival, pathogenicity and resistance to the host defences achieved through this differential protein expression[56]. In 2023, an uncharacterized adhesin, the surface colonization factor (Scf1) of *C. auris* was identified; its expression supports adhesion to inert and biological surfaces and covers isolates from all five clades[57].

Biofilm formation. Biofilm formation is a process observed in various microorganisms, including fungi such as *C. albicans*, through which a

scaffold composed of colonies of fungi surrounded by a dense, protective extracellular matrix is formed. It involves multiple steps that begin with the attachment of yeast cells to surfaces and their proliferation, followed by yeast-to-hyphal transition, which adds to the overall architectural stability of the biofilm and extracellular matrix production by constituent cells afterwards. This culminates in the maturation of a robust three-dimensional biofilm structure, eventually paving the way for dispersion[58]. Biofilm formation enables the adhesion of *Candida* species to surfaces, serving as a source of fungal dissemination through disperser cell release, a process where non-adherent fungal cells disperse into the bloodstream, allowing for dissemination into organs and the establishment of new biofilms[58]. The bulky extracellular matrix of biofilms also provides protection against the host immune system and antifungal agents[59]. These stimuli induce the biofilm constituent cells to reinforce their defence mechanisms[59]. The biofilm is maintained through the presence of persister cells, which are resistant to several antifungals[58].

Invasion and dissemination. Invasion by *Candida* species involves two primary mechanisms: active penetration and induced endocytosis. Active penetration is a vital process in intestinal invasion that relies on secreted hydrolytic enzymes, notably candidalysin, to disrupt epithelial cells and their tight junctions. Induced endocytosis, a process that mainly relies on the interaction between fungal and host surface proteins to allow for endocytosis, is observed in interactions with stratified epithelial and endothelial cells where agglutinin-like sequence proteins are involved[60]. Once in the bloodstream, the *Candida* species adheres to and crosses endothelial layers for dissemination via interaction with cadherins and unidentified endothelial receptors, a process still only partially understood due to limited in vivo studies[60,61]. *C. albicans* secretes various enzymes, facilitating adhesion, invasion, nutrient sequestration, and host cell damage and contributing to immune evasion[62]. The most notable enzyme is candidalysin, a hyphal cytolytic protein responsible for host cell damage[63] and immune system evasion, highlighting its significance in systemic infections[63].

Immune evasion. *C. albicans* employs diverse strategies to evade the immune system. It can conceal cell-wall components to avoid detection by the host immune system in response to metabolic cues, such as low iron and oxygen levels and elevated lactate levels, reducing β-glucan

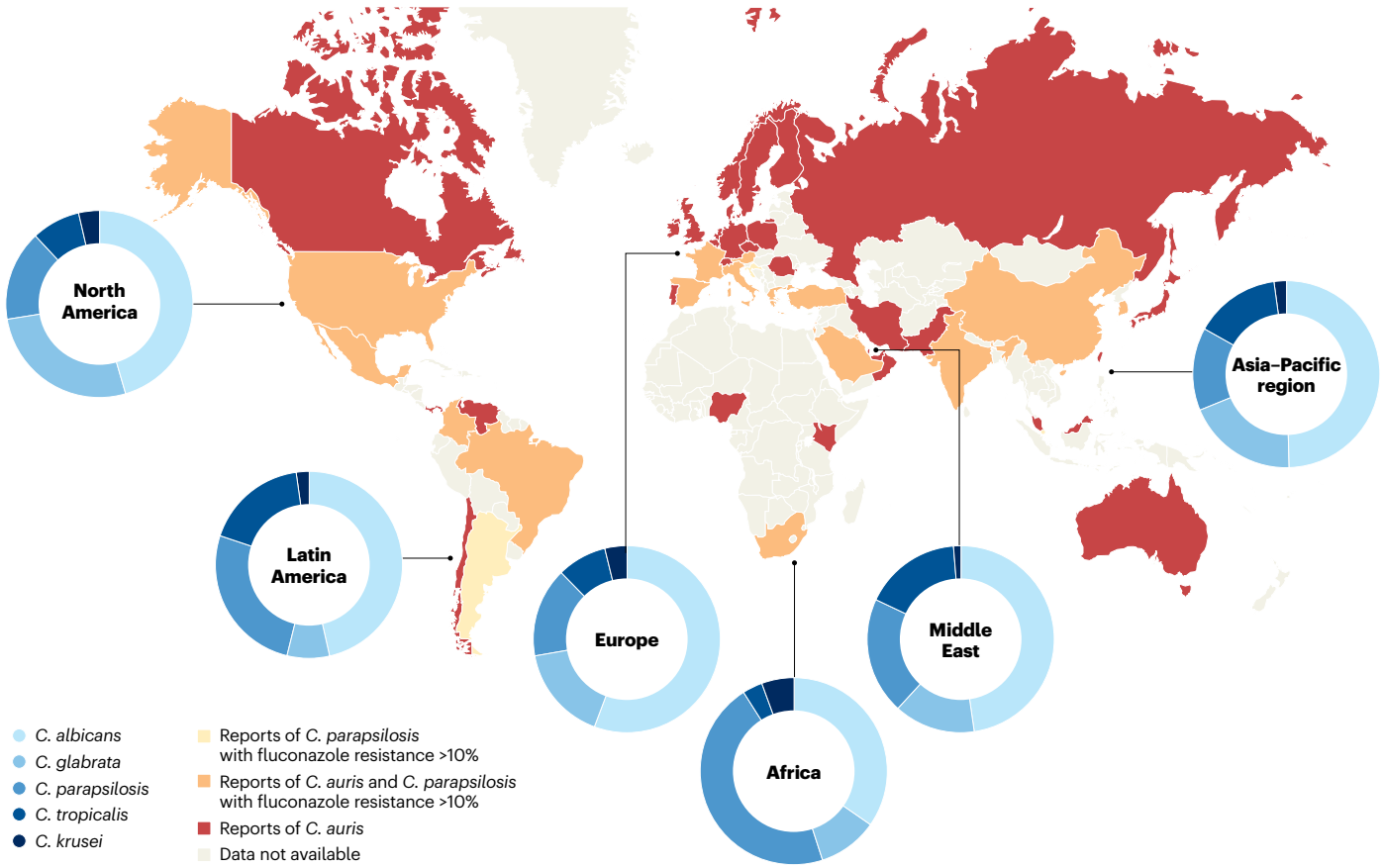
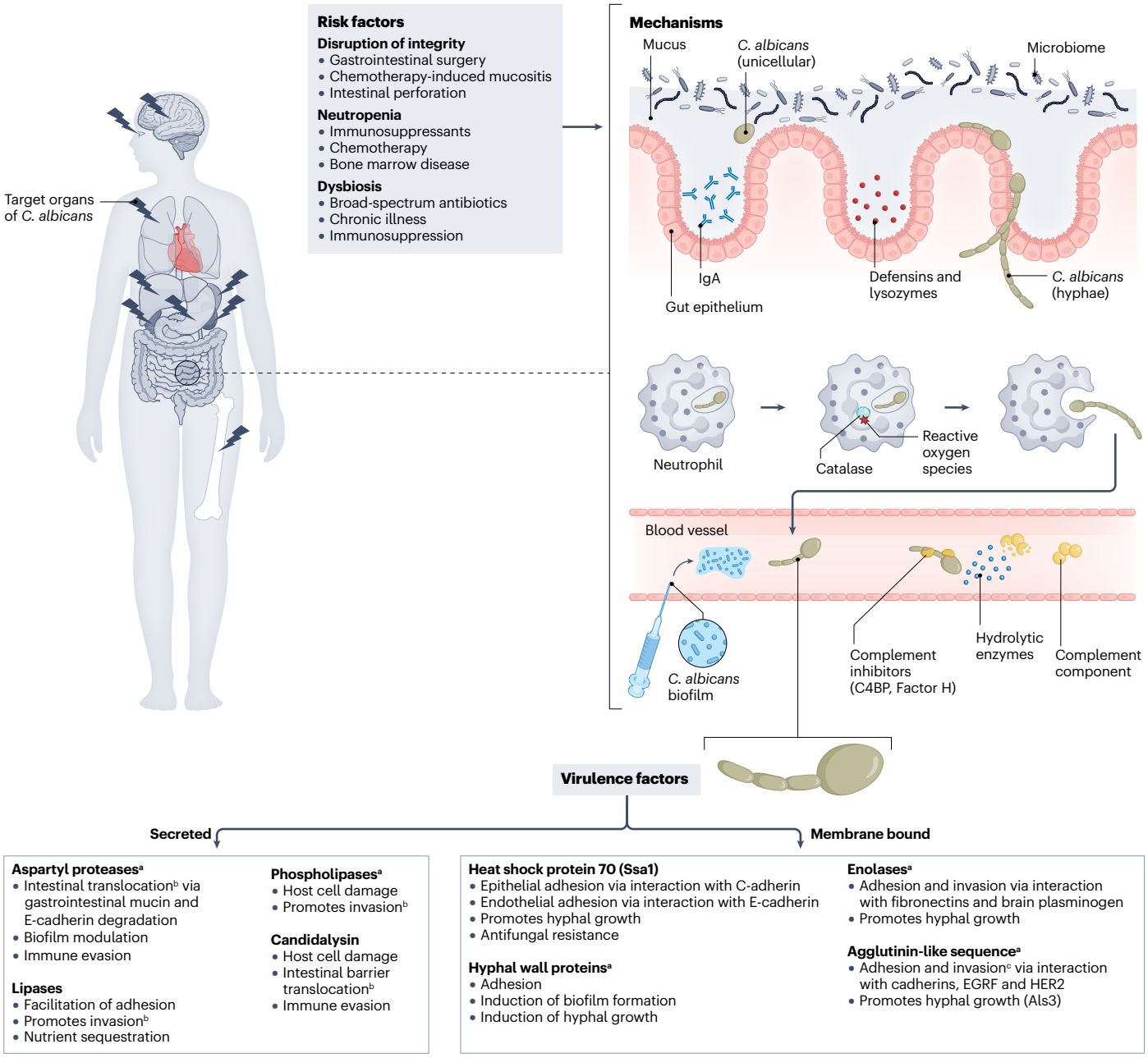


Fig. 1 | Geographical variation in the distribution of *Candida* species and countries reporting the major species of concern. Species distribution as well as resistance rates are influenced by numerous factors, including the health-care system, in combination with the frequency of vulnerable patient groups, antimicrobial treatment and prophylaxis policies, demographics, and environmental factors such as climate and agricultural practices. The global spread of *Candida auris* and fluconazole-resistant *Candida parapsilosis* strains are worrisome developments, with both species causing large hospital outbreaks of resistant strains. Species distribution data as pie charts in different world regions are comprised from refs. 9,46,183. Countries reporting the isolation of *C. auris* and/or fluconazole resistance rates >10% in *C. parapsilosis* are highlighted in the map, with data from refs. 139,144, updated with data from refs. 140,184,185 (*C. auris*) and refs. 145,186 (*C. parapsilosis*).



expression[64]. It also secretes enzymes like phospholipases, lipases and proteases to neutralize immune proteins, namely antibodies and enzymes like defensins and lysozymes[65]. Moreover, *C. albicans* can avoid phagocytosis through pH neutralization and hyphal transition[66] and rupturing of phagocytes via intra-endosomal growth. Additionally, it triggers pyroptosis, a form of inflammasome-mediated cell death[65].

The host response

Recognition. The immune response against *C. albicans* begins when any phagocyte recognizes intracellular and extracellular pathogen-associated molecular patterns through variable receptors, most notably C-type lectin receptors (CLRs)[67] (Fig. 3). These receptors act synergistically to expand recognition and enhance the response to the pathogen with species-specific recognition patterns[67]. Recognition triggers signalling cascades, leading to the release of cytokines and chemokines, which increase phagocyte recruitment and strengthen phagocyte-mediated killing mechanisms[67] (Fig. 4). A CLR-mediated signalling pathway is vital in the immune response to *Candida* species[68]. This is highlighted by the fact that defects in TLR and complement pathways do not substantially increase susceptibility to infection as opposed to deficiency in caspase recruitment domain-containing protein 9 (CARD9), a key molecule in the CLR pathway[69]. This deficiency is characterized by an increased susceptibility to infection[67], with central nervous system (CNS) tropism due to CARD9-dependent microglial cytokine secretion to recruit the phagocytes called neutrophils[70].

Fig. 2 | Virulence factors and immune evasion in *Candida albicans*. Multiple defence mechanisms prevent *Candida albicans* from reaching the bloodstream and seeding into target organs. The intestinal mucosa, coated with mucins, IgA and secreted antimicrobial peptides (for example, defensins and lysozymes), the tight junction between its enterocytes, and the gut microbiome are all involved. Once risk factors affect these lines of defence, this fungus can cross the intestinal surface and disseminate. Multiple virulence factors are employed to ensure adhesion and invasion, some membrane bound, others secreted[53,62]. On its way to its target organs, *C. albicans* is faced with multiple obstacles set by the immune system, which are evaded by the fungus in various ways[65,66]. *C. albicans* cells not yet engulfed by phagocytes secrete proteases to hydrolyse microbicidal proteins released by neutrophils such as lysozymes and immunoglobulins. Factor H and C4BP (inhibitors of the complement system) on the cell surface of *C. albicans* are used, via interaction with complement regulator surface-acquiring proteins, to evade the complement system[73]. Once inside a phagosome, *C. albicans* secretes superoxide dismutase and catalase to neutralize reactive oxygen species inside the phagosome. C. *albicans* can also transition to a hyphal form and expand, rupturing the phagosome and the phagocyte. [a]Morphology-dependent differential expression. [b]Active penetration. [c]Induced endocytosis.

Neutrophils. Neutrophils are an important defence against *Candida* species, and deficiencies in the number of neutrophils or their function correlate with mortality[68,71]. After identifying *C. albicans*, various killing strategies are employed[72] depending on fungal morphology[65] (Fig. 3). Oxidative mechanisms produce reactive oxygen species and reactive nitrogen species that cause damage to cellular structures and molecules through oxidative stress, ultimately leading to cell death. Non-oxidative killing includes trace element sequestration and secretion of microbicidal proteins[72,73]. Neutrophil extracellular traps effectively capture and kill *C. albicans* in both yeast and hyphal forms[72,73]. The weak association between mutations in oxidative pathways and invasive candidiasis highlights the significance of these non-oxidative mechanisms[72,74].

Other phagocytes. Other phagocytes, such as monocytes, macrophages and dendritic cells, contribute to protection against invasive candidiasis, though their role is secondary to neutrophils (Fig. 3). Recognition of *Candida* species primarily relies on the dectin 1 receptor on neutrophils, monocytes and macrophages[73]. Given their ability to act as antigen-presenting cells and consequently activate the adaptive immune system, macrophages and dendritic cells are involved in bridging the gap between the innate and adaptive immune system[73]. Natural killer cells also exhibit direct and indirect candidacidal activity[68,73]. Monocytes engage in phagocytosis and early production of pro-inflammatory cytokines within the initial hours of infection[75]. They also support neutrophils by enhancing their survival and candidacidal activity through the secretion of cytokines that trigger signalling cascades related to these processes such as IL-15 (refs. 73,76). Macrophages employ similar defence mechanisms to neutrophils[73] and rely on multiple receptors, mainly CX3CR1, CCR1 and dectin 1, to upregulate their candidacidal activity[77,78]. Monocytes and macrophages also confer lymphocyte-independent protection through epigenetic reprogramming, resulting in innate memory through a dectin 1-dependent pathway[79]. Dendritic cells are capable of phagocytosing yeast and hyphae and secrete distinct cytokine patterns in response to different fungal morphologies. A critical subset, $CD11b^+$ dendritic cells, are involved in defending against invasive candidiasis by producing inflammatory mediators, directly killing fungi, and priming neutrophil candidacidal activity[73]. Platelets may be involved in fighting *Candida* given that thrombocytopenia is a known risk factor for candidiasis; however, the mechanisms through which they act are yet to be fully elucidated[80]. Certain combined genetic variants, including those encoding the displayed receptors and cytokines, substantially increase candidaemia susceptibility. Immunogenetic mapping, enabling risk stratification, is a potential area of study to guide further investigation into antifungal prophylaxis and intensified regimens[81].

Mechanisms underlying complications

Invasive candidiasis often results from pathogen-mediated damage, host-mediated damage or both[82]. The virulence factors of *Candida* combined with the immune response lead to organ damage and failure[83]. In addition to candidaemia, which can lead to sepsis and shock in some patients, tissue-specific differences in immune response have a major role in pathology. For instance, murine models have demonstrated that early immune cell recruitment to the infection site is critical, with varying speeds in different organs[75]. The liver and spleen recruit quickly, while the kidneys are slower to recruit immune cells. Kidneys are among the most affected organs, with studies on mouse models revealing colonization post-infection and higher colony-forming unit counts correlating with mortality[84]. Neutropenia enables *Candida* dissemination but excessive neutrophil accumulation later in infection leads to immunopathology or host tissue damage secondary to an exaggerated neutrophilic response rather than pathogen clearance. This process often necessitates the use of steroids such as in patients reporting abdominal pain in the setting of hepatosplenic candidiasis. Multiple receptors (that is, CR3 and galectin 3) and cytokines are implicated as major drivers of excessive neutrophilic response[85,86]. This interplay can be observed in the case of hepatosplenic candidiasis[87]. It is hypothesized that prolonged neutropenia enables fungal dissemination, with immune reconstitution shifting towards a T helper 1 or T helper 17 cell-mediated response[87], contributing to pathogenesis. This partly explains some studies demonstrating benefit in patients receiving steroids as adjuvant to antifungal therapy[88]. This phenomenon is also observed in intra-abdominal candidiasis, in which both *Candida*-induced damage during immune weakness and local neutrophilic immune reactions lead to significant inflammation, eventually causing candidaemia and dissemination[82].

Diagnosis, screening and prevention

Infections and manifestations

Understanding the spectrum of invasive candidiasis is essential to guide a diagnostic and treatment approach. Invasive candidiasis is an over-arching term that encompasses candidaemia, a documented culture-confirmed BSI, which accounts for more than half of cases in observational epidemiological studies and clinical trials and several related but less well-studied syndromes such as acute or chronic disseminated candidiasis among patients with neutropenia or intra-abdominal candidiasis[89]. Invasive candidiasis poses an initial diagnostic challenge due to the absence of specific signs and symptoms, especially when there is candidaemia without a clear focus of infection[4]. This ambiguity is exacerbated in vulnerable newborns, in whom identifying invasive candidiasis is particularly difficult based on the vague, multiple and non-specific symptoms and signs of sepsis such as jitteriness, reduced spontaneous activity, apnoea, bradycardia, temperature instability

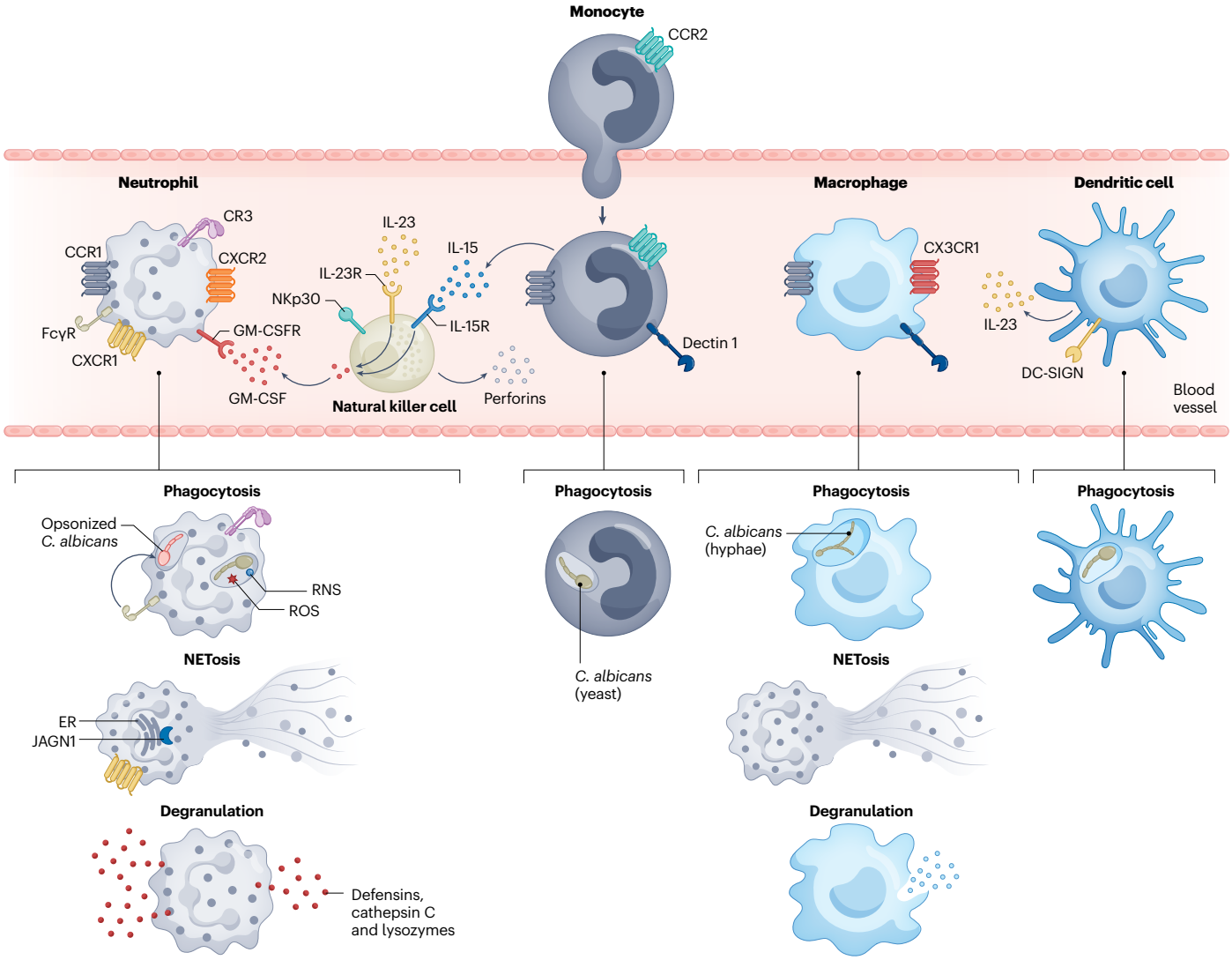


Fig. 3 | Phagocyte-led immune response to invasive candidiasis. Oxidative mechanisms generate reactive oxygen species (ROS) and reactive nitrogen species (RNS), while non-oxidative mechanisms generate microbicidal proteins and extracellular traps. Both are used by macrophages and neutrophils to clear *Candida* morphologies[65,66]. Other phagocytes secrete cytokines to maintain neutrophil activation and candidacidal activity, like IL-15 by monocytes and IL-23 by CD11b$^+$ dendritic cells, leading to the secretion of granulocyte–monocyte colony-stimulating factor (GM-CSF) by natural killer cells in response[66]. Neutrophils express CXCR2 and CCR1 for early and late recruitment[62], respectively. As for effector mechanisms, neutrophils express CR3 for neutrophil extracellular trap (NET) activation and phagocytosis of non-opsonized *Candida albicans*[66], FcγR for recognition and phagocytosis of opsonized cells[66], and CXCR1 receptor and JAGN1 endoplasmic reticulum (ER) proteins for non-oxidative mechanisms[62]. Dendritic cells express DC-SIGN for phagocytosis of *Candida* morphologies[63]. Macrophages express CX3CR1 surface receptors for survival and recognition[66]. Natural killer cells express NKp30 surface receptors for perforin release[66]. CCR1 recruits and CCR2 transmigrates monocytes to infection sites[66].

and respiratory distress[90]. In general, clinicians should consider the possibility of invasive candidiasis in patients with a compatible sepsis or severe sepsis syndrome, especially when the patient has underlying medical conditions, and predisposing risk factors (Box 2) as well as an inadequate response to empirical broad-spectrum antibiotic treatment.

When a source of infection is identified or when the *Candida* infection spreads to deep organs, specific signs may manifest. This provides a more concrete starting point for clinicians, enabling them to investigate and control the source and tailor their management approach accordingly. Disseminated disease demands a more comprehensive and multidisciplinary evaluation. *Candida* endophthalmitis, a severe sight-threatening manifestation (strictly defined as chorioretinitis with an extension of the surrounding inflammation into the vitreous or a vitreous abscess manifesting as intravitreal fluff balls), occurs in up to 1.8% of patients with candidaemia[91]. Some guidelines recommend dilated eye exams for all patients with candidaemia and others only recommend this for those with visual symptoms[92–94].

However, the targeted screening approach does not consider the lack of established visual symptoms or that sedated or intubated critically ill patients cannot articulate symptoms, and thus risks missing cases and an opportunity to prevent vision loss[95]. *Candida* endocarditis is less frequent (1–2%) and an echocardiographic evaluation is generally indicated when the risk factors and clinical features of a patient suggest this diagnosis[4]. CNS involvement occurs in 15–20% of premature neonates with invasive candidiasis[96,97]; thus, lumbar puncture and cranial imaging are standard procedures when neonatal candidaemia is suspected in this population[98]. Moreover, in patients with neutropenia caused by myeloablative chemotherapy, a syndrome of acute disseminated candidiasis may occur, manifesting as a BSI with skin lesions (including nodules, ecthyma gangrenosum (invasion of the fungus around small blood vessels of the skin with impaired blood supply resulting in gangrenous ulcers), purpura fulminans (clotting within small blood vessels of the skin, which manifests initially as skin bruising and progresses to skin necrosis) and leukocytoclastic vasculitis (inflammation of small blood vessels of the skin, which results in deep red to purple lumps)) and multiple organ involvement[51]. Chronic disseminated candidiasis (or hepatosplenic candidiasis) can occur during recovery from neutropenia, manifesting as a low-grade fever and right upper quadrant pain, often associated with a palpable and tender liver and splenomegaly[99]. Imaging may reveal multiple focal abnormalities in the parenchyma of the liver, spleen, kidneys and, sometimes, lungs[99]. Blood cultures are less frequently positive in this syndrome; thus, a tissue biopsy may be needed for confirmation of the diagnosis[99]. Intra-abdominal candidiasis has been sub-classified into several clinical syndromes, including primary peritonitis, secondary peritonitis or intra-abdominal abscess from a variety of sources, including infected pancreatic necrosis and cholecystitis or cholangitis[100].

The source of invasive candidiasis can be the skin, gastrointestinal tract or genitourinary tract[101]. Figure 5 gives an overview of the proposed pathophysiological mechanisms during the onset of an infection. However, candidaemia may have a predominant gastrointestinal origin even when caused by species such as *C. parapsilosis*, which are frequently recovered from skin samples[101]. Proliferation with subsequent dominance of the skin and/or the mucosal flora by *Candida* species, detected as culture-positive colonization of multiple body sites, is a significant predisposing factor for invasive disease[102] (Fig. 5). Several mycobiome studies have shown that positive blood

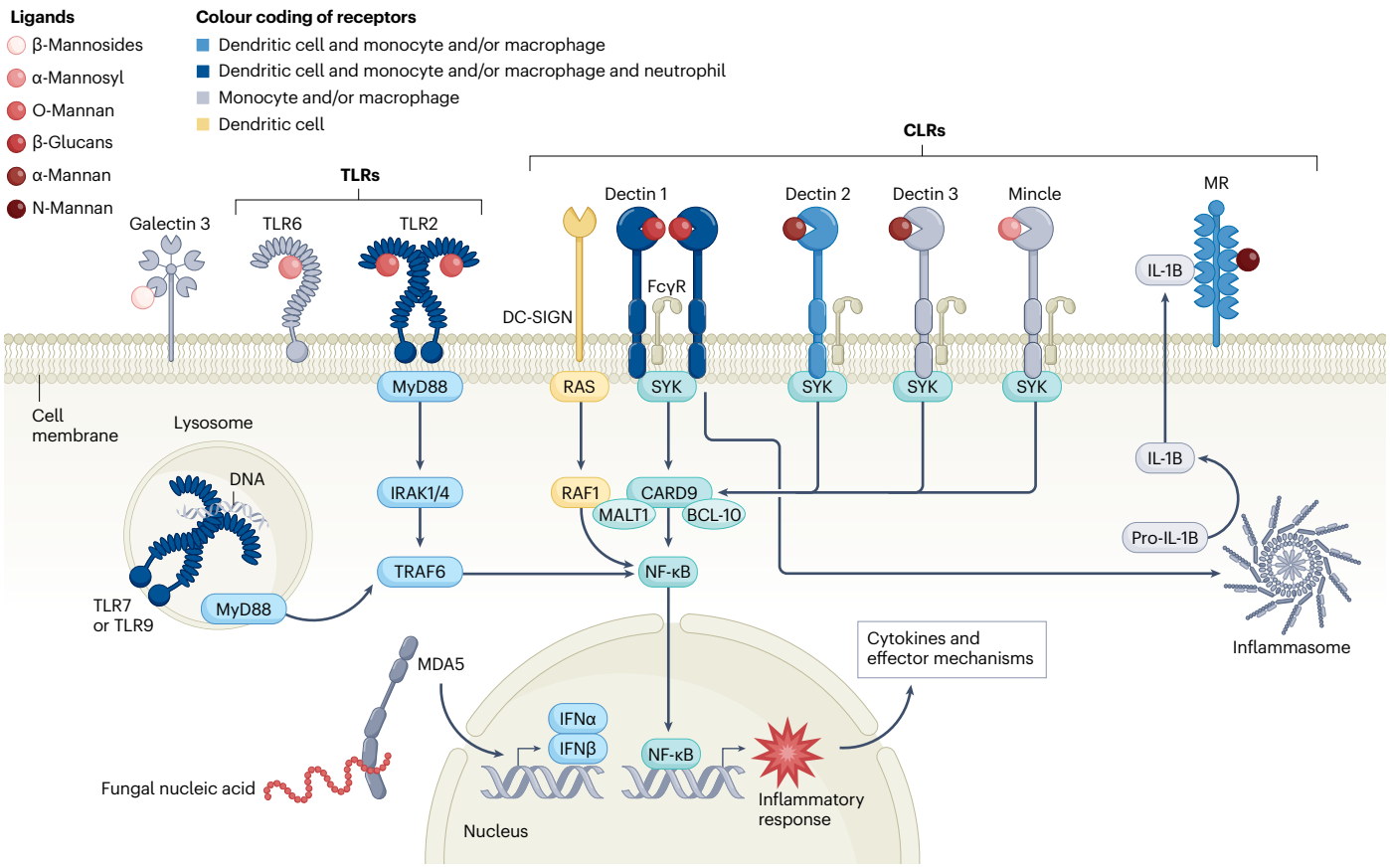


Fig. 4 | Important receptors and signalling pathways against invasive candidiasis. Multiple pattern recognition receptors are involved in recognition and immune response modulation, each responsible for a *Candida* molecule[67]. Some of these receptors are displayed uniquely on certain phagocytes and work in synergism to modulate the immune response. Pattern recognition receptors are either surface receptors, such as C-type lectin receptors (CLRs) and some Toll-like receptors (TLRs), or intracellular receptors such as intracellular TLRs and the RIG-I-like receptors MDA5 and NLRPs, important in cytosolic recognition. RIG-I-like receptors have been recently found to play a role in the detection of fungal RNA, causing the release of type I interferons (IFNα and IFNβ). Inflammasomes induced via SYK activation result in cleavage of pro-IL-1B to IL-1B[67]. The main signalling pathways are CLR–SYK–caspase recruitment domain-containing protein 9 (CARD9) and TLR–MyD88–IRAK4 (ref. 67). Both converge to NF-κB activation, causing activation of these cells and cytokine release. MR, mannose receptor.

cultures are preceded by increases in the relative abundance of single *Candida* species, whereas patients who do not develop candidaemia maintain a more diverse skin or gut mycobiome[103,104].

Diagnosis

The timely and targeted diagnosis of *Candida* infections is an ongoing challenge. This is primarily because clinical manifestations are not specific and yeasts are part of the normal and healthy human microbiota, and therefore may act as colonizers and/or true pathogens[93]. While cultures and microscopic examination from sterile body specimens are the gold standard of diagnosis, isolating yeast organisms from sputum or non-sterile body sites does not necessarily indicate infection[93]. In addition, these conventional diagnostic tests lack diagnostic sensitivity and often do not yield a positive result promptly, leading to a delay in proper therapy[105]. Furthermore, patients with disseminated infections may have negative blood cultures; therefore, vigilance is required in the interpretation of superficial cultures, antigen tests, molecular-based assays and the presence of antibodies[10].

Table 1 provides an overview of the strengths and limitations of the various laboratory-based assays. Clinical management differentiates between screening (to detect potential disease indicators) and diagnostic-driven strategies (to establish the presence or absence of disease)[93]. The selection of diagnostic tests usually depends on the patient population, pretest probability of disease, laboratory staff and regional expertise. There is no single test that meets all diagnostic requirements and covers all fungi; thus, a 'puzzle diagnostic approach' is recommended[2]. Diagnostic accuracy varies among available tests and usually depends on the studied patient population, specimens, and defined cut-off values of test results, and finally on disease stage[10]. Non-culture-based assays for invasive candidiasis display uncertainty when interpreting results as they are associated with high sensitivity and less specificity (Table 1). Biomarkers that detect either fungal metabolites or fungal DNA can be used to assist in the diagnosis rather than to establish a definitive diagnosis. Mannan and antimannan IgG tests and *C. albicans* germ tube antibody assays have been associated with limited sensitivity and specificity; for anti-*C. albicans* germ tube antibodies, better sensitivity has been reported for diagnosis of deep-seated candidiasis versus candidaemia[106].

Fungal infections, as part of any differential diagnosis, should be considered in patients presenting with clinical signs and symptoms of an infection and who do not respond to antibiotic treatment[93]. Depending on the specimen, the usual approach consists of microscopy, culture, serology and/or molecular-based techniques. Species identification must be determined from all yeasts detected from sterile body sites as the results guide antifungal treatment[107]. Nowadays, matrix-assisted laser desorption ionization-time of flight is the choice for fast and specific species identification[3,4]. LMICs with sub-optimal laboratory facilities and missing infrastructures should focus on the incorporation of point-of-care tests for diagnosis. simplify clinical diagnostic criteria and develop LMIC-specific guidelines for cost-effective management of invasive fungal infections[108]. The susceptibility of *Candida* spp. to the currently available antifungal agents is generally predictable if the species is identified[107]. Antifungal susceptibility testing (AFST) is recommended in patients who do not respond to treatment, when a new or rare species is isolated, or finally when dealing with emerging pathogens such as *C. auris*. Clinical breakpoints (CBPs) and epidemiological cut-off values may help in the management of an infection[107,109]. CBPs are determined by minimal inhibitory concentration (MIC) ranges that classify organisms as susceptible or not and are used in the clinical setting to advise on patient therapy[107]. Epidemiological cut-off values are defined as the MIC that incorporates most of the wild-type strains in a population and excludes non-wild-type strains, notably isolates that are likely to contain a resistant mutant[107]. Typically, antifungal resistance in *C. albicans* is uncommon, while triazole and echinocandin resistance among *N. glabrata* isolates have emerged[107]. Due to clinical outcome data, *C. parapsilosis* species complex was reclassified as being susceptible to echinocandin[47]; however, fluconazole-resistant *C. parapsilosis* species complex has emerged due to various clonal outbreaks, mainly affecting adults naive to azole treatment[110].

Initial considerations upon diagnosis

The identification of potential sources (that is, intra-abdominal abscesses) is essential in the diagnosis and treatment of invasive candidiasis as drainage and repeat cultures of these sites, when available, will guide the duration of therapy[92]. Blood cultures should be obtained

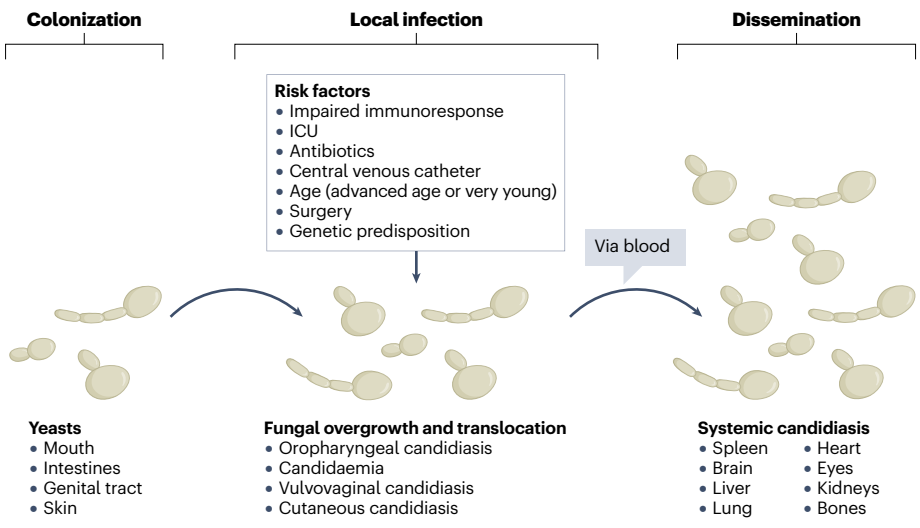


Fig. 5 | Proposed pathomechanisms in the onset of an infection. In the context of invasive candidiasis, the gastrointestinal tract is the primary site of origin, as *Candida albicans* is a well-established colonizer. Gut bacteria are involved in restraining the growth of *C. albicans*[187]. However, excessive antibiotic use disrupts this balance, increasing *Candida* spp. and inducing their pathogenic hyphal form[52]. The intestinal mucosal lining acts as a critical barrier against fungal invasion and prevents dissemination through physical and biochemical means[187]. Various factors can compromise the integrity of this barrier[187]. Another risk factor is a breach in skin integrity often associated with central venous catheters, where *C. albicans* can form biofilms, facilitating dissemination[52]. When these physical barriers are breached, phagocytes serve as the frontline defenders against *Candida* spp. However, in the setting of immunosuppressive therapies, this line of defence is easily compromised, facilitating dissemination. ICU, intensive care unit.

Table 1 | Overview of laboratory-based diagnosis[2,10,93,115,118,180,181]

Diagnostic test	Advantages	Limitations	Comments
Microscopy	Proof of infection, if positive from sterile body specimens; rapid turnaround time and broad applicability	Lack of genus or species identification; needs a high amount of fungal cells to be visible; low sensitivity	Fluorescent brighteners increase sensitivity and typical fungal morphologies may enable tentative diagnosis; histopathology shows tissue invasion and inflammation
Culture	Supports species identification and antifungal susceptibility testing; easy and cheap	Low sensitivity in candidaemia (~50%); difficult to distinguish between colonization and infection from non-sterile body sites; time-consuming	Not all fungi grow in culture (for example, *Pneumocystis jirovecii*); detection of polymicrobial infections is supported by using chromogenic media
Serology	The 1,3-β-D-glucan assay has a high negative predictive value; in invasive infections, sensitivity and specificity range from 75% to 80% and 60% to 80%, respectively; the combined mannan antigen and antimannan antibody assay displays a sensitivity of 89% and specificity of 63%	1,3-β-D-glucan is a fungal cell-wall component, and therefore is a panfungal marker with no differentiation between the various fungi; does not cover Mucorales and *Cryptococcus*; false positive results may occur when treated with intravenous immunoglobulin and albumin; may decline slowly despite appropriate therapy; mannan antigen and antimannan antibody assay shows limited specificity due to normal commensalism or colonization by *Candida* species	Specificity improves using serial samples; different companies provide various thresholds; most useful in patients in the intensive care unit; lower sensitivity for *Candida krusei* and *Candida parapsilosis*; the sole use of mannan antigen test shows variable sensitivity (52–85%) and specificity (86–98%), whereas antimannan antibodies give sensitivity of 57–80% and specificity of 60–87%
Molecular assays	Culture-dependent systems are highly sensitive and specific; have a short turnaround time and contain fully automated platforms; culture-independent tests have a moderate sensitivity and specificity, with high negative predictive value; enable a broad range of pathogen detection	Detect only defined *Candida* species; panfungal PCRs are less helpful from non-sterile sites and display poor performance in mixed infections; metagenomic assays are highly sensitive but less specific (target all microorganisms)	Fungal DNA isolation techniques are critical; best data when used in tissue-positive specimens; early detection of infection has been reported

daily or every other day to document clearance of the bloodstream[92]. Central venous catheters should be removed as soon as possible when presumed to have been the source of candidaemia as removal has been associated with decreased mortality[111]. Quantitative cultures from concurrently obtained catheter and peripheral blood cultures may be useful to determine the source[112]. Catheter removal alone is insufficient for treatment and concurrent antifungal therapy should be administered[92]. Persistent blood culture positivity following catheter removal and/or source control should prompt the search for other sites of infection (that is, endocarditis, septic thrombophlebitis). Infective endocarditis should be suspected in patients with persistent candidaemia. Predisposing conditions include prior bacterial endocarditis, prosthetic valves or intracardiac devices, and injection drug use[113]. Abdominal candidiasis and hepatic, splenic or renal abscesses may occur as a complication of candidaemia. Persistent fevers or chills, abdominal symptoms, or liver enzyme abnormalities suggest the need for abdominal imaging[92]. These lesions are distinct from hepatosplenic candidiasis — a form of chronic disseminated candidiasis apparent after neutrophil recovery in those with prior neutropenia and which requires prolonged antifungal therapy.

Screening and prevention

Candida colonization is a risk factor for the development of invasive candidiasis among patients in the ICU[93]. Hence, the role of screening for *Candida* colonization as part of the evaluation of a *Candida* scoring system (bedside assessment integrating total parenteral nutrition, surgery, multifocal *Candida* colonization and severe sepsis[102]) was investigated in several studies[114,115]. A published meta-analysis indicated that critically ill patients with sepsis who are colonized with *Candida* species are more likely to develop invasive candidiasis (odds ratio 3.32, 95% CI 1.68–6.58) than non-colonized patients[116]. The negative predictive value of *Candida* colonization was high (96.9%, 95% CI 92.0–98.9%) but the positive predictive value was low (9.1%, 95% CI 5.5–14.6%). At low pretest likelihoods, positive predictive values and negative predictive values are usually low and high, respectively. Candidaemia is a low-prevalence disease and varies from <1% to 10%[117]. The role of screening for the panfungal marker 1,3-β-D-glucan in serum was investigated in blood culture-negative intra-abdominal candidiasis[118]. 1,3-β-D-glucan testing was superior to *Candida* score and anticipated the diagnosis of blood culture-negative candidiasis[118]. Overall, there is little evidence that the performance of antigen screening is of great clinical value[119] either for starting or stopping antifungal treatment in the ICU.

Besides standard infection control practices, there are no specific non-pharmaceutical measures in preventing invasive candidiasis, with the exception of *C. auris*. This multidrug-resistant species is a health-care-associated organism with the potential of outbreaks[120] and may remain in the environment for weeks[121]. If a patient is colonized or infected, special prevention measures, such as placing the patient in a single room, disinfecting the rooms with chlorine-based products, and wearing gloves and gowns to deliver care, are highly recommended[120].

Overall, targeted antifungal prophylaxis may have a role in reducing the burden of disease in vulnerable individuals[91]. Currently, there is no commercialized anti-*Candida* vaccine approved for human use[122].

Management

The approach to management initially consists of an assessment of the extent of infection, attempts to reduce the fungal burden by removal of infected intravascular catheters or devices, drainage of intra-abdominal abscesses, and reversal of immunosuppression whenever possible. After initial steps to reduce fungal burden, the treatment of candidaemia consists of early and appropriate antifungal therapy and removal of a central venous catheter likely to be associated with the infection. Treatment options include antifungal drugs such as

echinocandins, azoles and amphotericin B formulations, which target essential aspects of the fungal organism (echinocandins target the production of cell-wall β-D-glucan; azoles target fungal production of ergosterol; amphotericin B formulations target extraction of ergosterol from fungal cells) (Table 2). No benefit to combination therapy has been demonstrated[123]. In patients with *Candida* BSI, repeat daily blood cultures should be performed until documentation of clearance of candidaemia[92].

Management of specific manifestations

Neutropenia. In patients with neutropenia, echinocandins (caspofungin, micafungin, anidulafungin or rezafungin) are recommended as first-line therapeutic options[92,93,124]. Lipid amphotericin B formulations are potential alternative agents in cases of intolerance or resistance to echinocandins[92,93]. Triazoles should not been prescribed as initial therapy in patients with neutropenia given the frequent use of this class in prophylaxis and the increased prevalence of non-*albicans Candida* species, which are commonly azole resistant[92,93]. Following clinical improvement, identification of the causal *Candida* isolate and demonstration of azole susceptibility, stepping down from an echinocandin to a triazole is recommended for the completion of therapy given the oral bioavailability of triazoles[92]. In the absence of absorption concerns, an oral formulation can be used for the completion of therapy. In patients with neutropenia, the duration of candidaemia treatment in the absence of endovascular or metastatic complications of infection should be a minimum of 14 days of therapy after documented clearance of candidaemia[125]. Resolution of attributable signs and symptoms of infection is needed prior to completion of therapy.

Non-neutropenia. In patients without neutropenia, echinocandins are also recommended as first-line agents[92,125]. However, patients who are not critically ill, demonstrate clinical stability and are known not to have an infection caused by a fluconazole-resistant organism may receive fluconazole, voriconazole or isavuconazole. Patients intolerant to or with an infection that is refractory or resistant to echinocandins or azoles may require an amphotericin B formulation[92,93]. The principles of step-down therapy and duration of therapy in the non-neutropenic population are like those in the neutropenic population.

Ocular infection. Ocular infection may occur following candidaemia with haematogenous seeding of the eye or an exogenous form following surgical intervention, trauma or extension of corneal infection[92,93]. Endophthalmitis refers specifically to involvement of the vitreous space (between the lens and retina) and is a sight-threatening infection[92]. In such cases, vitrectomy and intravitreal injection of antifungal therapy (amphotericin B deoxycholate or voriconazole) are necessary. Concurrent systemic treatment with fluconazole or voriconazole for 4–6 weeks is preferred unless concerns for resistance arise. Patients with chorioretinitis (inflammation of the choroid and retina) can be treated with systemic antifungal therapy alone for 4–6 weeks.

Intra-abdominal infections

Abdominal infections most frequently occur following gastrointestinal surgery, intestinal perforation or acute necrotizing pancreatitis[92,93]. Treatment entails surgical intervention and antifungal therapy. Drainage of abscesses, relief of biliary obstruction and repair of any intestinal perforation are key tenets of management[100]. Echinocandins are the recommended first-line therapeutic agents, although fluconazole can be used in those who have not had a fluconazole-resistant species identified[92,93]. A lipid amphotericin B formulation may also be used but is not preferred due to the nephrotoxicity of these agents[92,93]. Therapy should continue until signs and symptoms of peritonitis have resolved, source control has been achieved and for a minimum of 2 weeks. The low concentration of echinocandins in the peritoneal tissue has been

Table 2 | Treatment options for invasive candidiasis[51,92,93,138,161,182]

Antifungal	Frequency	Route	Notes and considerations
Fluconazole	Daily	PO, IV	Liver test abnormalities, drug–drug interactions (strong inhibitor of CYP2C19 and moderate inhibitor of CYP2C9 and CYP3A4), xerosis, cheilitis and alopecia with long-term use
Voriconazole	Twice daily	PO, IV	Liver test abnormalities, significant drug–drug interactions (strong inhibitor of CYP3A4, moderate inhibitor of CYP2C19 and weak inhibitor of CYP2C9), photosensitivity, hallucinations and confusion, and photopsia; voriconazole is extensively metabolized by CYP2C19 and CYP3A4, and genetic polymorphisms cause wide variations in pharmacokinetics
Isavuconazole	Daily	PO, IV	Liver test abnormalities, electrolyte abnormalities; drug–drug interactions as a moderate inhibitor of CYP3A4
Caspofungin	Daily	IV	Infusion reaction with rapid administration, liver test abnormalities; drug interactions potentially mediated via organic anion-transporting polypeptides such as OATP-1B1
Micafungin	Daily	IV	Infusion reaction with rapid administration, liver test abnormalities; drug–drug interactions with cyclosporine and sirolimus, other interactions uncommon
Anidulafungin	Daily	IV	Infusion reaction with rapid administration, liver test abnormalities; drug–drug interactions uncommon
Rezafungin	Weekly	IV	Infusion reaction with rapid administration, electrolyte abnormalities; drug–drug interactions uncommon
Flucytosine	Four times daily	PO, IV	Haematological abnormalities, including agranulocytosis, anaemia, pancytopenia, abdominal pain, diarrhoea and nausea; drug–drug interactions not apparent but agents with similar toxicity may be additive
Amphotericin B deoxycholate	Daily	IV	Systemic therapy: infusion reactions, nephrotoxicity, renal tubular abscess, hypokalaemia
			For bladder irrigation, amphotericin B is used in sterile water and administered as continuous bladder irrigation daily for 5 days
Liposomal amphotericin B	Daily	IV	Infusion reactions, nephrotoxicity, renal tubular abscess, hypokalaemia

Alternative dosing strategies may be needed in selected clinical circumstances such as in the intensive care unit and kidney impairment or drug–drug interactions. IV, intravenous; PO, per os.

shown to possibly predispose to the emergence of resistance in some *Candida* species[126].

Urinary tract

Infection of the kidneys may occur through haematogenous dissemination or via ascending infection from bladder infection. Most patients with candiduria are asymptomatic and the cultured yeasts merely represent colonization[127]. Differentiating between colonization and bladder infection is difficult. Patients with persistent candiduria should undergo evaluation of the kidneys with ultrasonography or computed tomographic imaging to evaluate for renal involvement. Asymptomatic candiduria should not be treated except in those with neutropenia, very-low-birth-weight infants (<1,500 g) or those undergoing urological procedures as asymptomatic candiduria is common, is infrequently of clinical consequence and often relapses[92,93]. Of the currently available triazoles, only fluconazole achieves significant concentrations in urine and is the preferred agent in symptomatic cases or those necessitating treatment. A course of 14 days is recommended for complicated *Candida* urine infection[92,93]. In cases of fluconazole-resistant *Candida* species, amphotericin B deoxycholate is recommended for 1–7 days with or without flucytosine. Monotherapy with flucytosine can be used as an alternative, for 7–10 days in cystitis and 14 days in pyelonephritis with sufficiently high concentrations being achieved in urine to prevent the emergence of resistance[92,93].

Meningitis

CNS involvement may occur as a manifestation of disseminated candidiasis, which is most common in premature neonates, in those with intracranial devices or following craniotomy[128]. Treatment of meningitis consists of amphotericin B deoxycholate or lipid amphotericin B combined with flucytosine. CNS devices associated with infection should be removed. Therapy should be continued until clinical improvement, and repeated cerebrospinal fluid assessment documenting improvement for a minimum of 2 weeks should be performed[92,93].

Endocarditis

A combined surgical and medical approach is recommended for cases of *Candida* endocarditis. Treatment with an echinocandin or lipid amphotericin B with or without flucytosine is recommended. Higher doses of echinocandins are often used, although data supporting this approach are limited. Surgical resection of the involved valve and any associated perivalvular abscesses is recommended[92,93]. Following clinical improvement and blood culture sterilization, the patient can be transitioned to chronic triazole therapy. Long courses of therapy are common following surgery and, in those unable to undergo surgical intervention, lifelong therapy is recommended due to the high rate of relapsing infection[113].

Hepatosplenic candidiasis

The initial treatment of hepatosplenic candidiasis consists of an echinocandin for 2 weeks or a lipid amphotericin B formulation. Following improvement, step-down therapy with a triazole is indicated[92,93]. Fever and other symptoms may be prolonged even with effective antifungal therapy. The natural history of hepatosplenic candidiasis is highly dependent upon the host immune response. With resolution of neutropenia, radiographic findings may transiently worsen. Clinical improvement with antifungal therapy may be seen over several weeks, although some patients may have persistent symptoms lasting months. Patients with persistent fever despite antifungal therapy, without evidence of other infectious aetiologies, may benefit from adjuctive corticosteroid therapy[88]. Antifungals should be continued until resolution of radiographic hepatosplenic lesions or calcification is observed upon follow-up abdominal imaging.

Specific treatment issues of various *Candida* species

***C. albicans*.** Large-scale epidemiological studies have shown a resistance rate to fluconazole of 0–5%[129]. Patients with prior mucocutaneous candidiasis receiving long-term triazole therapy may have higher rates of fluconazole resistance with overexpression of genes encoding lanosterol 14α-demethylase (*ERG11*) and efflux transporters (*MDR1*, *CDR1* and *CDR2*) being the most frequently identified mechanisms; amino acid substitutions are less frequently observed[130]. In general, this species is susceptible to the echinocandins and amphotericin B[107].

***N. glabratus*.** Infections by *N. glabratus* are more common in patients with prior azole exposure and this organism often requires higher fluconazole dosing strategies even when MICs are in the susceptible or dose-dependent susceptible or intermediate category[107,131]. *N. glabratus* exhibits frequent resistance to azoles mediated by changes in drug efflux (Cdr1 and Cdr2)[132]. Echinocandins are the recommended first-line therapy for *N. glabratus*, although resistance may develop on therapy[133]. The ability of *N. glabratus* to develop resistance to multiple drug classes (triazoles and/or echinocandins) has been associated with a 'mutator phenotype' caused by a mismatch repair defect[134]. In sites with *N. glabratus* resistance rates exceeding 10%, empiric lipid amphotericin B formulations may be appropriate while awaiting identification and susceptibility results.

***P. kudriavzevii*.** *P. kudriavzevii* is resistant to fluconazole due to changes within *ERG11*, although typically remains susceptible to alternative triazoles[9]. Voriconazole resistance is uncommon in North America and Europe but may be increasing in Central and South America[135,136]. Echinocandin resistance is rare; therefore, echinocandins remain the treatment of choice. This species exhibits decreased susceptibility to amphotericin B; hence, higher doses are needed for treatment[135,136].

***Clavispora lusitaniae*.** *C. lusitaniae* is frequently resistant to amphotericin B. This species is generally susceptible to azoles and echinocandins; therefore, these agents are recommended for treatment[136].

***C. parapsilosis*.** When treating *C. parapsilosis*, echinocandin MICs are frequently elevated due to a naturally occurring Pro-to-Ala substitution within hot spot 1 of the FKS1p[137]; however, for severe infections, echinocandins remain the recommended first-line therapy[138]. Fluconazole resistance has emerged within the past 5 years and is rapidly spreading[47,139].

***C. auris*.** *C. auris* emerged as a significant pathogen threatening global health. Most isolates of *C. auris* are resistant to fluconazole (due to *ERG11* mutations) with variable susceptibility to other azoles. Echinocandins are recommended as initial treatment[140]. *C. auris* can develop resistance quickly and multidrug-resistant isolates (resistance to both azoles and echinocandins)[141] as well as pan-resistant isolates (additional resistance to amphotericin B) have been reported in 13–35% of isolates[142,143]. Flucytosine resistance is still relatively uncommon[144,145]. Persistence in health-care facilities and failure of ammonium

compounds to eradicate *C. auris* from environmental surfaces has serious implications for infection control and prevention.

Quality of life

Invasive candidiasis in health-care settings is an infection with high consequences with overall and attributable mortality of ~30–40%[146]. As survivors are often critically ill, they often experience severe post-ICU deconditioning, prolonged recovery, morbidities such as end-organ damage, including renal or hepatic failure, or complications of metastatic disease such as osteomyelitis[147]. They can also experience sequelae that can be disabling and severely affect their quality of life (QOL) such as blindness when the eye is affected through dissemination[91]. Even less aggressive forms of invasive candidiasis in the ambulatory setting, such as chronic mucocutaneous disease and recurrent vulvovaginal candidiasis, can have severe cosmetic, psychological, social and functional consequences that greatly impact the QOL of affected patients[148].

There is very limited research specifically focusing on QOL in patients with candidaemia and much of it focuses on macro pharmaco-economic analyses of different antifungal therapies[149,150] or pre-emptive therapy models[151,152], where more aggressive antifungal therapy upfront, coupled with de-escalation and administration of antifungals based on positive markers or risk factors, has been shown to be favourable and cost-effective in increasing quality-adjusted life years.

As most cases of invasive candidiasis occur in ICU settings in critically ill patients, one can glean effects on QOL from the critical care literature, showing that both survivors of critical illness and their caregivers experience severe and prolonged physical, mental and social problems following the illness[153,154].

Survivors of invasive candidiasis, particularly those with end-organ disease such as endophthalmitis, osteomyelitis or endocarditis, often deal with multiple medical problems and infection-related sequelae. Most notably, *Candida* endophthalmitis may result in partial or complete vision loss[155]. Patients with end-organ disease are often exposed to prolonged courses of intravenous or oral antifungal therapy and may require close monitoring of laboratory parameters, management of adverse effects, and adjustments related to potential drug–drug interactions. Close monitoring of both the antifungals and the drugs used to manage their underlying illness is essential to ensure adequate therapy and avoid toxicity. These interactions are sometimes treatment limiting and can further decrease the QOL of the affected patient.

In the ambulatory space, chronic mucocutaneous candidiasis, which is often associated with genetic or endocrine disorders, can be severely disfiguring and limit both function and social interactions[156,157]. Although not strictly invasive, recurrent vulvovaginal candidiasis has clearly been shown to have profound effects on psychological and sexual wellness and health[158,159]. Further research on the effects of these infections on QOL is warranted.

Outlook

Most risk factors that predispose people to invasive candidiasis are unavoidable because they are directly related to the underlying diseases as well as their required treatment. Furthermore, infections are likely to increase due to improved survival of people with medically complex conditions[160], new and broader indications for immunosuppressive treatments[161], and the widespread use and expanded indications of novel immunomodulatory agents[162]. These agents may lead to collateral damage mainly affecting human defence mechanisms, which in turn facilitate fungal infections with pathogens of low virulence[163]. In addition, during the past few years, the population at risk expanded due to COVID-19-related C*andida* infections[164] and the emergence of fungal break-through infections[165].

An accurate and rapid diagnosis of invasive candidiasis is of critical importance; it is apparent that cultures alone detect only a subset of clinical diseases[3,4]. Presently, we have a wide diagnostic armamentarium to assist in the diagnosis of *Candida* infection by non-invasive methods but most tools lack either high sensitivity or specificity[10]. Supplementing these conventional techniques with novel molecular-based techniques is highly welcome in addition to understanding which patients will benefit from which test combination. The newest technologies, such as metagenomic next-generation sequencing (mNGS), are promising but must first prove their worth before entering routine clinical pathways[166]. One example of a mNGS platform is the Karius test, which detects cell-free DNA (cfDNA) from plasma of over 1,250 human pathogens, including bacteria, fungi and DNA viruses[167]. In comparison to pathogen-specific PCRs, cfDNA sequence testing is limited by poor sensitivity in localized infections, uncertain specificity (detection of cfDNA fragments may not be of clinical value), slow turnaround time and high costs[168]. However, such broad pathogen testing, even without a priori suspicion, may improve patient management and may support early antifungal treatment. An advantage seems to be that mNGS detection is less likely to be affected by prior antimicrobial treatment than traditional methods. So far, only few data exist covering mNGS and diagnosing invasive candidiasis; *C. tropicalis* was successfully identified in chronic disseminated candidiasis[169] and *Candida dubliniensis* was identified in four cases of meningitis[170]. Standardization and clinical validation processes are urgently needed and defining the best specimens for mNGS are further objectives.

From a clinical point of view, the best management of various fungal infections remains debatable. As an example, ophthalmological examination to evaluate for endophthalmitis is strongly recommended for patients with candidaemia by the European Society of Clinical Microbiology and Infectious Diseases guidelines for the diagnosis and management of *Candida* diseases in 2012 (ref. 3). This practice has been called into question due the relative infrequency of *Candida* endophthalmitis (<1%) and the unclear and potentially harmful effects of invasive interventions[171]. Targeted screening only in patients suffering from visual symptoms is recommended[172]. However, a systematic review and meta-analysis found that the incidence of ocular candidiasis (chorioretinitis or endophthalmitis) exceeded 10% with only 1.8% of patients meeting clinical criteria for *Candida* endophthalmitis[91].

In addition, the widespread use of prophylactic and empirical antifungal treatment in individuals who are critically ill remains a concern. Neither antifungal prophylaxis nor empirical therapy have reduced invasive candidiasis-related mortality in these settings[173]. The role of adapting the echinocandin dosing in patients in the ICU is an area for further investigation, specifically in patients exposed to extracorporeal membrane oxygenation, which may subsequently decrease the exposure to echinocandins[174]. Another controversial issue is the optimal timing to step down from intravenous to oral antifungal treatment. Improving antifungal stewardship, individualizing prophylaxis, tailoring treatment in special populations and monitoring for antifungal resistance are key strategies to improve outcomes and help mitigate the risk of losing antifungals to emerging resistance. Priorities for the next few years should also focus on the role of AFST as bundle measures to improve patient management. Relating thereto is the clinical

validation of the provided CBPs; in a multicentre, non-interventional study assessing MIC-guided and non-MIC-guided antifungal treatment regimens, no significant difference in outcomes was observed[109].

Several new antifungal agents in the pipeline or close to medical approval are fraught with uncertainties since the dual use of agents in the environment and in medical settings has been shown to be an important driver of resistance[175]. The new antifungal manogepix is an orphan drug with fast-track designations for invasive candidiasis, including for patients infected by echinocandin-resistant *C. parapsilosis* complex[176]. Manogepix inhibits the fungal GPI-anchored wall transfer protein 1 (Gwt1), a conserved acetyltransferase, and thus affects various physiological fungal processes. It is, however, noteworthy that the new plant fungicide aminopyrifen, which is structurally similar to manogepix and which also targets Gwt1, is already in use in agriculture[177]. Hence, we face the unfortunate situation that, in the medical setting, these drugs are promoted as 'novel' while already used in agriculture. Ibrexafungerp, a triterpenoid antifungal and first non-azole agent shows promising activity against azole-resistant and echinocandin-resistant *Candida* species. Various trials evaluating ibrexafungerp are ongoing. A One Health strategy is necessary to find solutions to these overlapping applications of antifungals to save lives, boost surveillance and provide AFST programmes for all the various disciplines. Moreover, the failure of disinfectants is an issue with unresolved questions such as the high prevalence of *C. parapsilosis* species complex in certain areas or the emergence of *C. auris* – why these species have such a tendency to survive on the hands of health-care workers and in the inanimate hospital environment needs further elucidation[178].

Understanding fungal epidemiology is of high importance. The emergence of multidrug-resistant *N. glabratus* and other species challenges antifungal treatment and infection control measures. So far, when and why *C. auris* leads to outbreaks versus single infections remain poorly understood. The role of climate change is another issue that needs to be studied to understand its potential effect on the emergence of new fungal species[179]. Finally, each country faces a different set of challenges depending on the local epidemiology of *Candida* infection, the prevalence of underlying risk factors (for example, HIV/AIDS), the structure of the health-care system, and the availability of diagnostic tools and antifungal treatment options[108]. High priority should be given to the strong implementation of WHO-recommended life-supporting measures such as access to simple diagnostic tests for detection and surveillance and to antifungal drugs for the treatment of invasive candidiasis[5].

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